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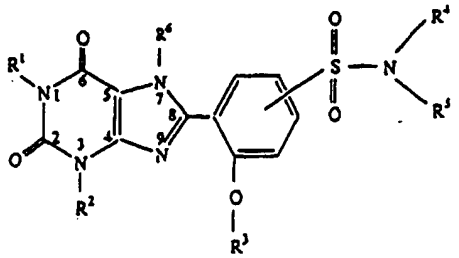

(I)

(57) Abstract

8–phenylxanthine derivatives of formula (I), wherein R^1, R^2 and R^3 each independently represent a hydrogen atom or an alkenyl, alkynyl, cycloalkyl or alkylcarbamoyl group or an alkyl group which may be unsubstituted or substituted, or a benzyl or phenyl group which may be unsubstituted or substituted either R^4 and R^5 together with the nitrogen atom to which they are attached form a 3 to 7–membered ring comprising a total of from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted, or R^4 is as defined for R^1 and R^5 represents an alkenyl, alkynyl, cycloalkyl, mono–or di–alkylamino, alkylcarbamoyl, aminocarboiminoyl group or a substituted alkyl group or R^5 represents a group of formula $-(CH_2)_n-R^7$ wherein n is an integer from 0 to 4 and R^7 represents a 3 to 7–membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted, R^6 represents a hydrogen atom or an alkyl group; and the $-SO_2NR^4R^5$ group is in the 4 or 5 position on the phenyl group; and pharmaceutically acceptable salts thereof, processes for their production, pharmaceutical compositions containing them and their use as phosphodiesterase 5 inhibitors.

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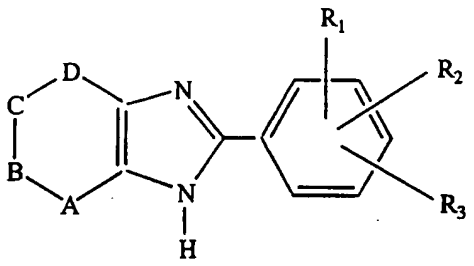
8-PHENYLXANTHINE DERIVATIVES AND THEIR USE AS PHOSPHODIESTERASE INHIBITORS

This invention relates to new therapeutically useful 8-phenylxanthine derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

It is known that some xanthine derivatives have been described in EP-A-435,811 as phosphodiesterase 4 (PDE 4) selective inhibitors and are useful in the treatment of diseases in which the production of cardiac stimulation is not appropriate.

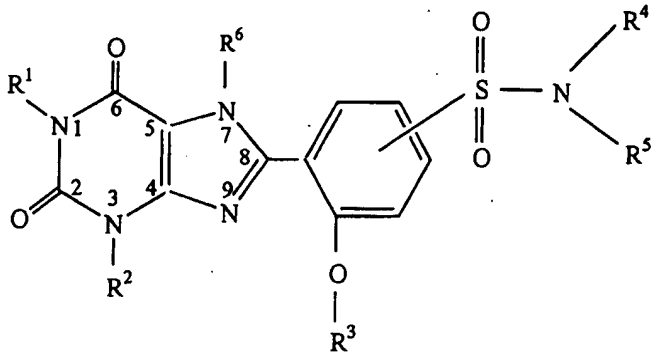
US 4,722,929 relates to new 2-phenyl-imidazoles of formula:



which are useful for the treatment of cardiac insufficiency.

We have now found that certain 8-phenylxanthine derivatives are potent and selective inhibitors of cyclic guanosine 3'-5'-monophosphate specific phosphodiesterase (cGMP specific PDE) and more particularly inhibitors of phosphodiesterase 5 (PDE 5), and for that reason, have efficacy in the treatment of angina, hypertension, congestive heart failure, stroke, asthma, male erectile dysfunction, female sexual dysfunction, glaucoma and irritable bowel syndrome.

Accordingly, the present invention provides compounds which are 8-phenylxanthine derivatives of formula (I):



(I)

wherein:

R^1, R^2 and R^3 each independently represent a hydrogen atom or an alkenyl, alkynyl, cycloalkyl or alkylcarbamoyl group or an alkyl group which may be unsubstituted or substituted by one or more halogen atoms or hydroxy, alkoxy, cycloalkyl, alkylthio, amino, mono- or di-alkylamino, oxo, hydroxycarbonyl, alkoxycarbonyl, carbamoyl or alkylcarbamoyl groups, or a benzyl or phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, hydroxy, alkylenedioxy, alkoxy, amino, mono- or di-alkylamino, nitro, cyano or trifluoromethyl groups;

either R^4 and R^5 together with the nitrogen atom to which they are attached form a 3 to 7-membered ring comprising a total of from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted by one or two halogen atoms or hydroxy, carbamoyl, hydroxycarbonyl, alkoxycarbonyl, amino, mono- or di-alkylamino groups or one or two alkyl groups which may be unsubstituted or substituted by one or more hydroxy, alkoxy, hydroxyalkoxy, hydroxycarbonyl, alkoxycarbonyl, amino or mono- or di-alkylamino groups, or

R^4 is as defined for R^1 and R^5 represents an alkenyl, alkynyl, cycloalkyl, mono-or di-alkylamino, alkylcarbamoyl, aminocarboiminoyl group or an alkyl group substituted by one or more halogen atoms or hydroxy, alkoxy, cycloalkyl, alkylthio, oxo, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, amino or mono- or di-alkylamino groups, or R^5

represents a group of formula

$$-(CH_2)_n-R^7$$

wherein n is an integer from 0 to 4 and R^7 represents a 3 to 7-membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted by one or more halogen atoms or hydroxy, phenyl, alkoxycarbonyl, amino, mono-alkylamino, di-alkylamino or hydroxycarbonyl groups or one or more alkyl groups which may be unsubstituted or substituted by one or more halogen atoms or hydroxy, phenyl, alkoxycarbonyl, amino, mono-or di-alkylamino or hydroxycarbonyl groups;

R^6 represents a hydrogen atom or an alkyl group;

and the $-SO_2NR^4R^5$ group is in the 4 or 5 position on the phenyl group;

or a pharmaceutically acceptable salt thereof.

The alkyl groups and moieties such as those present in the alkoxy, alkylcarbamoyl, mono- or di-alkylamino, carbamoyl alkyl, alkylthio, oxoalkyl, alkylenedioxy and alkoxycarbamoyl groups, mentioned in relation to the groups R^1 to R^7 are usually "lower" alkyl that is containing from 1 to 6 particularly from 1 to 4 carbon atoms, the hydrocarbon chain being branched or straight. Preferred alkyl groups, and where relevant alkyl moieties, include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl and t-butyl.

The alkenyl and alkynyl groups mentioned in relation to groups R^1 to R^7 are usually "lower" alkenyl and alkynyl groups, that is containing from 2 to 6 and particularly from 2 to 4 carbon atoms. Preferred alkenyl groups include vinyl, allyl and but-2-enyl groups. Preferred alkynyl groups included propargyl and butynyl groups.

The cycloalkyl groups mentioned in relation to the groups R^1 to R^5 are preferably C_{3-10} cycloalkyl groups, more preferably C_{3-7} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. The cycloalkyl-alkyl groups mentioned in relation to the groups R^1 to R^4 comprise an alkyl

group as specified above attached to a cycloalkyl group as specified above. Preferred cycloalkyl-alkyl groups include cyclopropylmethylene, cyclopropylethylene, cyclopentylmethylene, cyclopentylethylene, cyclohexylmethylene and cyclohexylethylene.

The halogen atoms mentioned in relation to the groups R^1 to R^5 and R^7 are preferably chlorine or fluorine atoms.

For compounds of the invention wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a ring, the ring may be saturated or unsaturated for example a piperidyl, pyrrolidyl, azetidinyl, aziridyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolyl, imadazolyl, imadazolidinyl, pyrazolinyl, diazacycloheptyl, indolinyl or isoindolinyl group, said group being substituted or unsubstituted. In preferred compounds of the invention the ring formed by R^4, R^5 and the nitrogen atom to which they are attached is a substituted or unsubstituted 5,6 or 7 membered ring such as a piperidyl, piperazinyl, morpholinyl, diazacycloheptyl, pyrrolidinyl or pyrazolyl group, most preferably a 4-hydroxypiperidyl, 3-carbamoylpiperidyl, 4-carbamoylpiperidyl, 3-carboxypiperidyl, 4-carboxypiperidyl, 3-ethoxycarbonylpiperidyl, 4-ethoxycarbonylpiperidyl, 4-dimethylaminopiperidyl, 4-(2-dimethylaminoethyl)-4-methylpiperidyl, piperazinyl, 3-methylpiperazinyl, 4-methylpiperazinyl, 2,5-dimethylpiperazinyl, 3,5-dimethylpiperazinyl, 4-ethylpiperazinyl, 4-propylpiperazinyl, 4-hydroxyethylpiperazinyl, 4-ethoxycarbonylpiperazinyl, 4-ethoxycarbonylmethylpiperazinyl, 4-(2-hydroxyethoxy)ethylpiperazinyl, morpholinyl, 4-methyl-1,4-diazacycloheptyl, 2-hydroxycarbonylpyrrolidinyl, 2-methoxycarbonylpyrrolidinyl or aminopyrazolyl group.

For compounds of the invention wherein R^5 represents a group of formula

$$-(CH_2)_nR^7$$

n may represent 0, 1, 2, 3, or 4, preferably 0, 1 or 2, R^7 may

be unsaturated or saturated and may represent for example a piperidyl, pyrrolidyl, azetidinyl, aziridyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, imidazolyl, imidazolidinyl, pyrazolinyl, indolinyl, isoindolinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, quinuclidinyl, triazolyl, pyrazolyl, triazolyl, tetrazolyl or thienyl group, which group may be substituted or unsubstituted. In preferred compounds of the invention wherein R^5 is a group of formula

$$-(CH_2)_nR^7$$

R^7 is a pyridyl, piperidyl, piperazinyl, quinuclidinyl, triazolyl or tetrazolyl group.

In compounds of the invention wherein R^5 is not a group of formula

$$-(CH_2)_nR^7$$

R^5 preferably represents a C_{1-6} alkyl group substituted by one or more halogen atoms or hydroxy, alkoxy, alkylthio, oxo, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or mono- or di-alkylamino groups.

In preferred compounds of the invention R^5 represents a 2-hydroxyethyl, 2-dimethylaminoethyl, propargyl, hydroxycarbonylmethyl, methoxycarbonylmethyl, 2,3-dihydroxy-n-propyl, N-acetyl-2-aminoethyl, carbamoylmethyl, cyclopentyl, pyridyl, pyridylmethyl, pyridylethyl, imidazolylpropyl, N-piperidylethyl, methylpiperidyl, 2,2,6,6-tetramethylpiperidyl, benzylpiperidyl, N-methyl-4-phenylpiperidyl-4-methyl, N-methyl-4-hydroxypiperidyl-4-methyl, N-benzyl-4-hydroxypiperidyl-4-methyl, N-benzyl-3-hydroxypiperidyl-3-methyl, N-ethoxycarbonyl-4-hydroxypiperidyl-4-methyl, N-methylpyrrolidinyl-2-ethylene, 3-β-D-glucopyranosyl, 2,2-cyclohexylidine-2-ethylaminoethyl, N-morpholinylethyl, N-morpholinylpropyl, 2-tetrahydrofurylmethyl,

methylpiperazinyl, quinuclidinyl, amidino, triazolyl or tetrazolyl group.

In preferred compounds of the invention R^1, R^2 and R^3 each independently represent an unsubstituted alkyl, monosubstituted alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl, phenyl, benzyl or substituted benzyl group. Most preferably, R^1, R^2 and R^3 each independently represent a methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, 2-chloroethyl, 2-hydroxyethyl, 2-methoxyethyl, 2-dimethylaminoethyl, 3-chloropropyl, 3-dimethylaminopropyl, 2-methyl-n-butyl, hydroxycarbonylmethyl, cyclopropyl, cyclopropylmethyl, cyclohexylmethyl, allyl, phenyl, benzyl or piperonyl group.

In preferred compounds of the invention wherein R^4 and R^5 together with nitrogen atom to which they are bonded do not form a heterocyclic ring, R^4 preferably represents a hydrogen atom or a substituted or unsubstituted alkyl group, most preferably a methyl group or hydroxyethyl group.

In preferred compounds of the invention R^6 represents a hydrogen atom or a methyl group.

In preferred compounds of the invention the $-SO_2NR^4R^5$ group is on the 5-position of the phenyl group to which it is attached.

Of outstanding interest are:

3-(3-butyl-1-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-4-propoxy-*N*-pyridin-4-ylbenzenesulfonamide,

4-ethoxy-3-(1-methyl-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-*N*-(1*H*-[1,2,4]triazol-3-yl)benzenesulfonamide,

3-(1-methyl-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-4-propoxy-*N*-(1*H*-[1,2,4]triazol-3-yl)benzenesulfonamide,

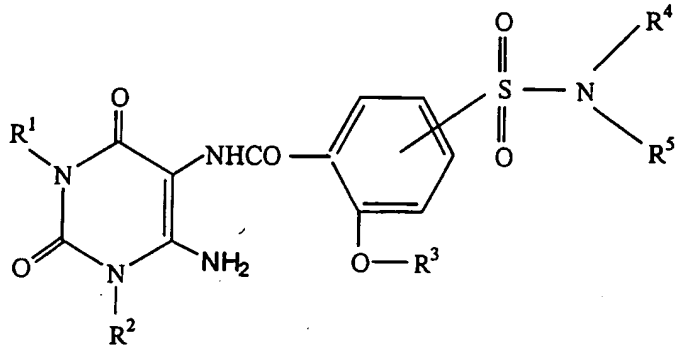
1-[3-(1-methyl-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-4-propoxybenzenesulfonyl]piperidine-4-carboxylic acid amide,

1-methyl-8-[5-(4-methylpiperazine-1-sulfonyl)-2-propoxyphenyl]-3-propyl-3,7-dihydropurine-2,6-dione,

3-butyl-1-methyl-8-[5-(morpholine-4-sulfonyl)-2-propoxyphenyl]-3,7-dihydropurine-2,6-dione,

8-{5-[4-(2-hydroxyethyl)piperazine-1-sulfonyl]-2-propoxypheny l}-1-methyl-3-propyl-3,7-dihydropurine-2,6-dione, and 1-methyl-8-[5-(piperazine-1-sulfonyl)-2-propoxyphenyl]-3-propyl-3,7-dihydropurine-2,6-dione.

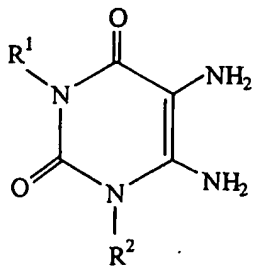
According to a feature of the present invention, the 8-phenyl xanthine derivatives of general formula (I) in which R^6 is hydrogen, are prepared by cyclizing an uracil compound of the general formula (II):



(II)

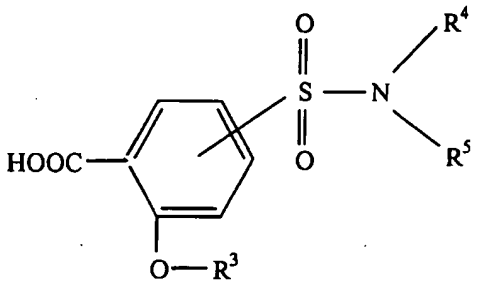
(wherein R^1, R^2, R^3, R^4 and R^5 are as hereinbefore defined) by application of cyclisation methods described in the literature, for example by heating with an aqueous solution of sodium or potassium hydroxide, preferably at the boiling point of the reaction mixture. After acidification of the reaction mixture the xanthine product of the general formula (I) is isolated in the known manner.

The 5-acylamido-uracil starting materials of general formula (II) are obtained by reaction of a corresponding 5,6-diaminouracil of the general formula (III):



(III)

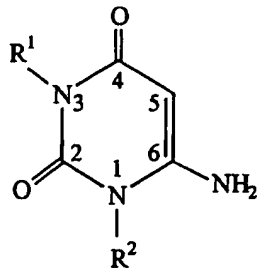
(wherein R^1 and R^2 are as hereinbefore defined) with a carboxylic acid of the general formula (IV):



(IV)

(wherein R^3, R^4 and R^5 are as hereinbefore defined) in an organic solvent preferably a polar aprotic solvent such as methylene chloride, dioxane or tetrahydrofuran, in the presence of a dehydrating agent such as 1,3-dicyclohexylcarbodiimide and a nucleophilic catalyst such as 4-dimethylaminopyridine, and at a temperature from 40°C to the boiling point of the solvent.

The 5,6-diaminouracils of general formula (III) can be prepared from a corresponding 6-aminouracil of the general formula (V):



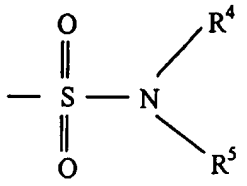
(V)

wherein R^1 and R^2 are as hereinbefore defined) by nitrosation at the 5-position using for example a mixture of sodium nitrite and acetic acid at a temperature between 10°C and 80°C, to give the corresponding 5-nitroso derivative, followed by reduction of the 5-nitroso compound using for example sodium dithionite in ammonium hydroxide aqueous solution at a temperature between 40°C and 90°C to give the diamino compound.

The 6-aminouracils of general formula (V) can be prepared

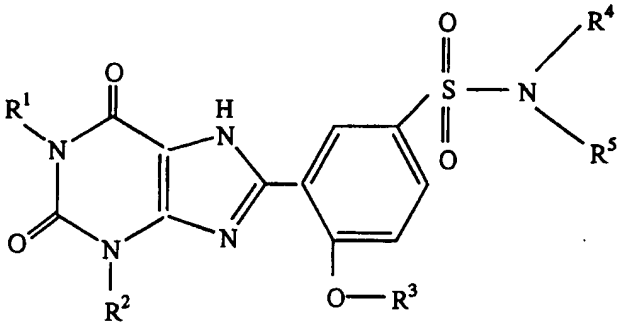
from the corresponding N,N'-disubstituted-urea by methods known per se, e.g. V. Papesch and E.F. Schroeder, J. Org. Chem., 16, 1879-90, (1951).

The 8-phenyl-xanthine derivatives of general formula (I) in which R^6 is hydrogen and the group of formula (VI):



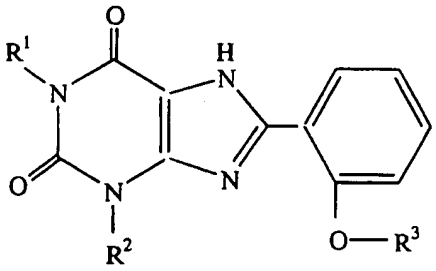
(VI)

(wherein R^4 and R^5 are as defined above) is in position five of the phenyl ring to which it is attached, viz. the 8-phenylxanthines of formula (VII):



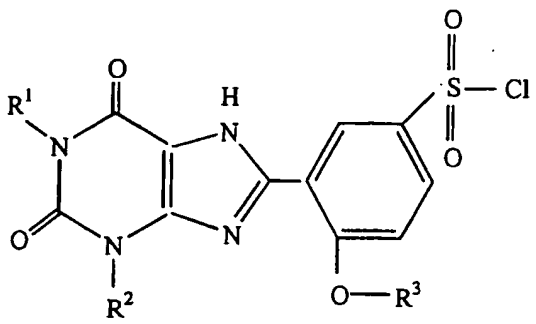
(VII)

in which R^1, R^2, R^3, R^4 and R^5 are as defined above, are also prepared according to a further feature of the present invention from the corresponding compound of formula (VIII):



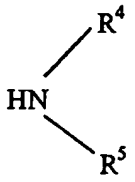
(VIII)

wherein R^1, R^2 and R^3 are as defined above, by reaction with an excess of chlorosulphonic acid, preferably under a nitrogen atmosphere and at a temperature from -5°C to 10°C and where the solvent is the same chlorosulphonic acid. In this manner, the sulphonyl chloride of formula (IX):



(IX)

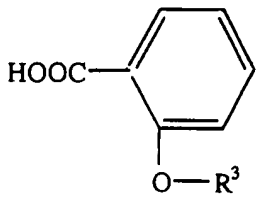
wherein R^1, R^2 and R^3 are as defined above, is obtained, which by further reaction with the corresponding amine (X):



(X)

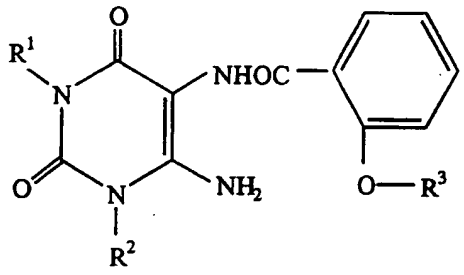
wherein R^4 and R^5 are as defined above, gives the 8-phenylxanthine derivative of general formula (I). The reaction is carried out in an organic solvent preferably a polar aprotic organic solvent such as dioxane, methylene chloride or tetrahydrofuran, at a temperature from 10°C to 40°C and in the presence of an organic base, preferably an amine base such as triethylamine. The thus obtained 8-phenylxanthine derivative is then isolated by the usual method known in the art.

The intermediate compounds of formula (VIII) can be prepared from the 5,6-diaminouracil of formula (III) and the corresponding carboxylic acid of the general formula (XI):



(XI)

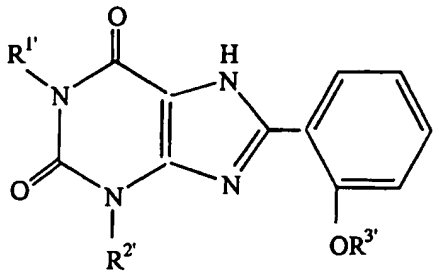
wherein R^3 is as defined above. In this case, a reactive derivative of the carboxylic acid (XI), as an acid halide or anhydride can also be used instead of the carboxylic acid itself. The reaction between the 5,6-diaminouracil of formula (III) and the reactive derivative of the carboxylic acid (XI) is carried out in a solvent, preferably a polar aprotic solvent, such as N,N-dimethylformamide, dioxane, acetone or tetrahydrofuran, in the presence of an organic base, preferably an amine base, such as triethylamine and at a temperature from 15°C to 40°C. Thus, the corresponding uracil compound of formula (XII):



(XII)

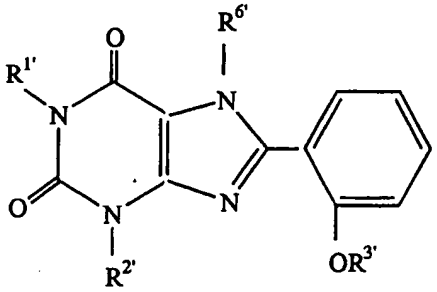
wherein R^1, R^2 and R^3 are as defined above, is obtained and is treated with an inorganic base such as sodium or potassium hydroxide as disclosed above for 8-phenylxanthine derivatives of formula (I). The corresponding compound of formula (VIII) is then obtained.

The 8-phenylxanthine derivatives of general formula (I) in which R^6 is an alkyl group and R^1, R^2 and R^3 are other than hydrogen, are prepared according to a further feature of the present invention, from the corresponding compound of formula (XIII):



(XIII)

(wherein $R^{1'}$, $R^{2'}$ and $R^{3'}$ are as defined for R^1, R^2 and R^3 except that are other than hydrogen) by reaction with an alkyl sulfate or alkyl halide (preferably alkyl iodide or bromide), in an inert solvent, preferably an aprotic polar organic solvent, such as N,N-dimethylformamide, dioxane or tetrahydrofuran, at a temperature from 20°C to 120°C and in the presence of an inorganic base such as sodium or potassium hydride or amide. In this manner, the corresponding alkyl intermediate of formula (XIV) is obtained.



(XIV)

wherein $R^{1'}$, $R^{2'}$ and $R^{3'}$ are as defined above, and $R^{6'}$ is an alkyl group. Compound (XIV) is then treated as compounds (VIII) and (IX) to obtain the corresponding 8-phenylxanthine derivative of formula (I) in which R^6 is an alkyl group.

The 8-phenylxanthine derivatives of formula (I) can be converted by methods known per se into pharmaceutically acceptable salts, preferably acid addition salts by treatment with organic or inorganic acids as fumaric, tartaric, succinic or hydrochloric acid. Also, 8-phenylxanthine derivatives of formula (I) in which there is the presence of an acidic group,

may be converted into pharmacologically acceptable salts with, for instance, alkali metals such as sodium or potassium by reaction with an alkali metal hydroxide. The acid or alkali addition salts so formed may be interchanged with suitable pharmaceutically acceptable counter ions using process known *per se*.

The cyclic GMP specific phosphodiesterase (PDE 5) was isolated from human platelet lysates by ion exchange chromatography using a Mono-Q column. The enzyme activity was determined using 0.25 μM [3H]-cyclic GMP as substrate. The purification of the enzyme and the assessment of the PDE 5 inhibitory activity of our compounds were performed essentially as described by Gristwood et al. (Br. J. Pharmacol. 105, 985-991, 1992).

The results from such test are shown in Table 1.

TABLE 1

Compound (*)	PDE 5 Activity from human tissues IC_{50} (nM)
16	9
37	12
38	3
75	9
86	35
96	19
133	12
154	58

(*) See structures in Tables 2 and 3.

As it can be seen from Table 1, the compounds of formula (I) are potent inhibitors of cyclic GMP specific phosphodiesterase (PDE 5) and are useful in the treatment of stable, unstable and variant angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel potency, peripheral vascular disease, vascular disorders (e.g. Raynaud's disease), stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, male erectile dysfunction, female sexual dysfunction and diseases characterized by disorders of gut motility, e.g. irritable bowel syndrome.

Accordingly, the 8-phenylxanthine derivatives of formula (I) and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such compound and/or salts thereof, may be used in a method of treatment of disorders of the human body which comprises administering to a

patient requiring such treatment an effective amount of a 8-phenylxanthine derivative of formula (I) or a pharmaceutically acceptable salt thereof.

The present invention also provides pharmaceutical compositions which comprise, as an active ingredient, at least a 8- phenylxanthine derivative of formula (I) or a pharmacologically acceptable salt thereof in association with a pharmaceutically acceptable excipient such as a carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight of the composition depending upon the nature of the formulation and whether further dilution is to be made prior to application.

Preferably the compositions are made up in a form suitable for oral, topical, nasal, rectal, percutaneous or injectable administration.

The pharmaceutically acceptable excipients which are admixed with the active compound, or salts of such compound, to form the compositions of this invention are well-known per se and the actual excipients used depend inter alia on the intended method of administering the compositions.

Compositions of this invention are preferably adapted for injectable and per os administration. In this case, the compositions for oral administration may take the form of tablets, retard tablets, sublingual tablets, capsules or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing the compound of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 2 and 500 mg of active ingredient or the equivalent amount of a salt thereof.

The liquid composition adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a

syrup. The suspensions may comprise an insoluble active compound of the invention or a pharmaceutically acceptable salt thereof in association with water, together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in pyrogen free aqueous media or other appropriate parenteral injection fluid.

Effective doses are normally in the range of 10-600 mg of active ingredient per day. Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

The invention is illustrated by the following Examples which do not limit the scope of the invention in any way.

EXAMPLE 1

a) To a solution of 1-propyl-3-methyl-5,6-diaminouracil (6.1 g; 0.031 moles) and triethylamine (3.1 g = 4.2 ml; 0.031 moles) in N,N-dimethylformamide (60 ml), another solution of 2-ethoxybenzoyl chloride (6.2 g; 0.034 moles) in N,N-dimethylformamide was slowly added at a temperature between 15°C and 20°C. The reaction mixture was stirred at room temperature for 20 hours, the solvent removed under reduced pressure, the residue treated with ethyl acetate and the resulting solution washed with water. After drying (Na_2SO_4) the solvent was removed in vacuo, the residual oil was treated with water (275 ml) and 2N sodium hydroxide aqueous solution (100 ml), and the mixture boiled under reflux for one hour. The resulting solution was cooled, washed with diethyl ether and the aqueous solution treated with acetic acid until acid pH (12 ml of acetic acid were necessary). The precipitated solid was collected by filtration, washed with water and diethyl ether and dried in a vacuum oven. 8-(2-Ethoxyphenyl)-1-methyl-3-propyl-3,7-dihydropurine-2,6-dione was obtained as a pale cream solid (4.7 g; 46% yield), m.p. 205-206°C (after recrystallization from isopropanol).

b) Chlorosulphonic acid (12.4 ml) was cooled at 0°C, and while stirring and maintaining nitrogen atmosphere, the compound obtained above (4.5 g; 0.0137 moles) was added over a period of 10 minutes. The mixture was stirred at room temperature for 15 hours, poured into ice-water (80 ml) and extracted with methylene chloride. The organic solution was washed with water, dried (Na_2SO_4), the solvent removed under reduced pressure and the residue collected by filtration with diethyl ether. A white solid of impure 4-ethoxy-3-(1-methyl-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)benzenesulphonyl chloride (4.8 g; 83% yield) was obtained which was purified by recrystallization from acetonitrile.

c) To a solution of 1-methylpiperazine (0.13 g; 0.00125 moles) and triethylamine (0.13 g; 0.00125 moles) in methylene chloride (30 ml), the above compound obtained in b) (0.53 g; 0.00125 moles) was slowly added and the resulting mixture stirred at room temperature for 20 hours. A solid crystallized which was collected by filtration, washed with methylene chloride and diethyl ether and dried. 8-[2-Ethoxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-methyl-3-propyl-3,7-dihydropurine-2,6-dione was obtained (0.43 g; 72% yield) which was purified by flash-chromatography with silica gel and a mixture of methylene chloride-methanol (15:1) as eluent. Melting point 174°C. (Compound 94 in Table 3).

EXAMPLE 2

A mixture of 1-benzyl-3-methyl-5,6-diaminouracil (0.36 g; 1.48 mmoles), 2-propoxy-5-(4-morpholinylsulphonyl)-benzoic acid (0.49 g; 1.48 mmoles), 1,3-dicyclohexylcarbodiimide (0.30 g; 1.48 mmoles) and 4-dimethylaminopyridine (0.18 g; 1.48 mmoles) in methylene chloride (15 ml), was boiled under reflux for 20 hours. The solvent was removed under reduced pressure, 2N sodium hydroxide aqueous solution (10 ml) was added and boiled under reflux for 2 hours. The reaction mixture was cooled, filtered and the residue washed with ethanol (4 ml). The filtered solution was treated with acetic acid until pH=6, then extracted with ethyl acetate and the organic solution washed

with water and brine. After drying (Na_2SO_4) the solvent was removed under reduced pressure and the residual orange solid (0.43 g) was purified by flash-chromatography with silica gel and ethyl acetate as eluent. 3-Benzyl-1-methyl-8-[5-(morpholine-4-sulphonyl)-2-propoxyphenyl]-3,7-dihydropurine-2,6-dione was obtained (0.30 g; 37.6% yield), m.p. 218°C . (Compound 158 in Table 3).

EXAMPLE 3

a) To a solution of 3-butyl-8-(2-ethoxyphenyl)-1-methyl-3,7-dihydropurine-2,6-dione (1.5 g; 0.0044 moles) in N,N-dimethylformamide (20 ml), a 60% dispersion in mineral oil sodium hydride (0.18 g; 0.0045 moles) was slowly added, and the resulting mixture stirred at room temperature until the release of hydrogen was completed. After heating at 60°C for 15 minutes, dimethyl sulfate (0.73 g; 0.0058 moles) was added, stirred at room temperature for 30 minutes and at 110°C for further 4 hours. The cooled reaction mixture was poured into water, extracted with ethyl acetate and the organic solution successively washed with water, 2N sodium hydroxide and water. After drying (Na_2SO_4) the solvent was removed under reduced pressure and the obtained solid treated with a mixture of diethyl ether-diisopropyl ether and collected by filtration. 3-Butyl-8-(2-ethoxyphenyl)-1,7-dimethyl-3,7-dihydropurine-2,6-dione was obtained (1.1 g; 70% yield) m.p. 135°C.

b) To chlorosulphonic acid (3 ml), the compound obtained above (1 g; 0.0028 moles) was slowly added at a temperature of 0°C while nitrogen atmosphere was maintained. After stirring at room temperature for 20 hours, the reaction mixture was poured into ice-water and extracted with methylene chloride. The organic solution was washed with water, dried (Na_2SO_4), the solvent removed <u>in vacuo</u> and the obtained residue treated with a mixture of diethyl ether-diisopropyl ether. 3-(3-Butyl-1,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-4-ethoxybenzenesulphonyl chloride was obtained as a white solid (1.1 g; 86% yield).

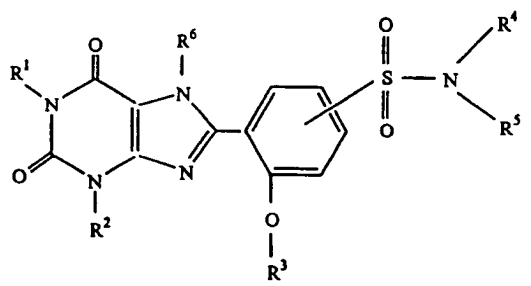
c) To a solution of 1-methylpiperazine (0.075 g; 0.00075

moles) and triethylamine (0.076 g; 0.00075 moles) in methylene chloride (25 ml) the above compound obtained in b) (0.34 g; 0.00075 moles) was slowly added and the resulting mixture stirred at room temperature for 20 hours. Methylene chloride (30 ml) was added, washed with water, decanted, the organic solution dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was treated with diethyl ether and collected by filtration when 3-Butyl-8-[2-ethoxy-5-(4-methylpiperazine-1-sulphonyl)phenyl]-1,7-dimethyl-3,7-dihydropurine-2,6-dione was obtained (0.31 g; 80% yield), m.p. 144°C. (Compound 101 in Table 3).

The 8-phenylxanthine derivatives of general formula (I) included in Tables 2 and 3, were prepared according to the processes disclosed in these Examples, but with the appropriate starting materials.

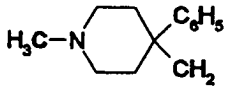
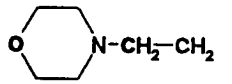
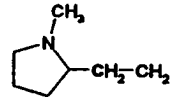
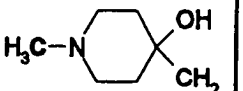
When the defined groups are changed under the conditions of the hereinbefore described processes or are inadequate to those processes, processes can be readily carried out by usual methods well known in the field of synthetic organic chemistry, for example, by protection of functional groups and elimination of protecting groups.

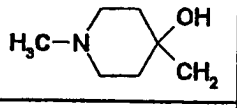
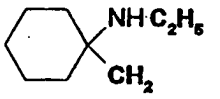
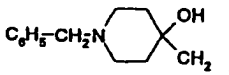
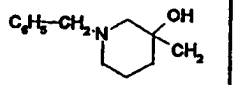
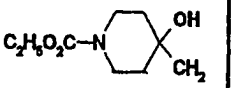
TABLE 2

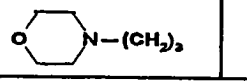


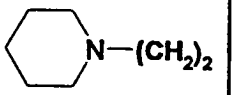
Compound	R^1	R^2	R^3	R^4	R^5	Sulfonamide position	R^6	Method Example	m.p. °C
1	CH_3	CH_3	C_2H_5	$HOCH_2-CH_2$	$HOCH_2-CH_2$	5	H	1	224
2	CH_3	C_3H_7	C_3H_7	$HOCH_2-CH_2$	$HOCH_2-CH_2$	5	H	1	172
3	CH_3	$i-C_4H_9$	C_3H_7	$HOCH_2-CH_2$	$HOCH_2-CH_2$	5	H	1	216
4	CH_3	C_3H_7	C_3H_7	H	propargyl	5	H	1	245
5	CH_3	CH_3	C_2H_5	H	$H_2N-CO-CH_2$	5	H	1	285
6	CH_3	C_3H_7	C_3H_7	H	$H_2N-CO-CH_2$	5	H	1	268
7	CH_3	C_3H_7	C_3H_7	H	HO_2C-CH_2	5	H	1	245
8	CH_3	C_3H_7	C_3H_7	H	$CH_3O_2C-CH_2$	5	H	1	229

Com-pound	R^1	R^2	R^3	R^4	R^5	Sulfon-amide position	R^6	Method Example	m.p. °C
9	CH_3	C_3H_7	C_3H_7	H	$HOCH_2$-CHOH-CH_2	5	H	1	255
10	CH_3	C_3H_7	C_3H_7	H	CH_3CONH-CH_2-CH_2	5	H	1	265
11	CH_3	C_3H_7	C_3H_7	H	cyclopentyl	5	H	1	242
12	CH_3	CH_3	C_2H_5	H	4-pyridyl	5	H	1	310
13	CH_3	C_3H_7	C_2H_5	H	4-pyridyl	5	H	1	302
14	CH_3	C_3H_7	C_3H_7	H	4-pyridyl	5	H	1	301-303
15	CH_3	n-C_4H_9	C_2H_5	H	4-pyridyl	5	H	1	295-296
16	CH_3	n-C_4H_9	C_3H_7	H	4-pyridyl	5	H	1	264
17	CH_3	cyclo-hexyl-CH_2	C_3H_7	H	4-pyridyl	5	H	1	246
18	C_2H_5	C_3H_7	C_3H_7	H	4-pyridyl	5	H	1	239
19	n-C_4H_9	n-C_4H_9	C_3H_7	H	4-pyridyl	5	H	1	197-199
20	CH_3	C_3H_7	C_3H_7	H	4-pyridyl-CH_2	5	H	1	257
21	CH_3	C_3H_7	C_3H_7	H	1-methyl-4-piperidyl	5	H	1	211

Com-pound	R^1	R^2	R^3	R^4	R^5	Sulfon-amide position	R^6	Method Example	m.p. °C
22	CH_3	C_3H_7	C_3H_7	CH_3	1-methyl-4-piperidyl	5	CH_3	1	198
23	CH_3	C_3H_7	C_3H_7	H		5	H	1	157
24	CH_3	C_3H_7	C_3H_7	H	1-benzyl-4-piperidyl	5	H	1	186
25	CH_3	C_3H_7	C_3H_7	C_2H_5	2-tetrahydro-furyl-CH_2	5	H	1	122
26	CH_3	C_3H_7	C_3H_7	H		5	H	1	174
27	CH_3	C_3H_7	C_3H_7	H		5	H	1	172
28	CH_3	C_3H_7	C_3H_7	H		5	H	1	223

Com-pound	R^1	R^2	R^3	R^4	R^5	Sulfon-amide position	R^6	Method Example	m.p. °C
29	CH_3	C_3H_7	C_3H_7	CH_3		5	H	1	200
30	CH_3	C_3H_7	C_3H_7	H		5	H	1	173
31	CH_3	C_3H_7	C_3H_7	H		5	H	1	117
32	CH_3	C_3H_7	C_3H_7	H		5	H	1	115
33	CH_3	C_3H_7	C_3H_7	H		5	H	1	132
34	CH_3	C_3H_7	C_3H_7	H	4-methyl-1-piperazinyl	5	H	1	159
35	CH_3	CH_3	C_2H_5	H	3-quinuclidinyl	5	H	1	277-279
36	CH_3	C_3H_7	C_3H_7	H	3-quinuclidinyl	5	H	1	189

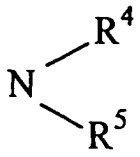
Compound	R^1	R^2	R^3	R^4	R^5	Sulfonamide position	R^6	Method Example	m.p. °C
37	CH_3	C_3H_7	C_2H_5	H	1,2,4-triazol-3-yl	5	H	1	228
38	CH_3	C_3H_7	C_3H_7	H	1,2,4-triazol-3-yl	5	H	1	229
39	CH_3	cyclohexyl-CH_2	C_3H_7	H	1,2,4-triazol-3-yl	5	H	1	245
40	C_2H_5	C_3H_7	C_3H_7	H	1,2,4-triazol-3-yl	5	H	1	223
41	CH_3	CH_3	C_2H_5	H	tetrazol-5-yl	5	H	1	256-258
42	CH_3	C_3H_7	C_2H_5	H	tetrazol-5-yl	5	H	1	224-226
43	CH_3	C_3H_7	C_3H_7	H	tetrazol-5-yl	5	H	1	189-190
44	CH_3	n-C_4H_9	C_3H_7	H	tetrazol-5-yl	5	H	1	181-182
45	n-C_4H_9	n-C_4H_9	C_3H_7	H	tetrazol-5-yl	5	H	1	204-206
46	CH_3	C_3H_7	C_3H_7	H	$HOCH_2$-CH_2	5	H	1	260
47	CH_3	C_3H_7	C_3H_7	H		5	H	1	148

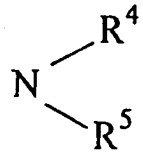
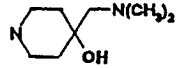
Com-pound	R^1	R^2	R^3	R^4	R^5	Sulfon-amide position	R^6	Method Example	m.p. °C
48	CH_3	C_3H_7	C_3H_7	H		5	H	1	182
49	CH_3	C_3H_7	C_3H_7	H	$(CH_3)_2NCH_2-CH_2$	5	H	1	215
50	CH_3	C_3H_7	C_3H_7	CH_3	$(CH_3)_2NCH_2-CH_2$	5	H	1	130
51	CH_3	i-C_4H_9	C_3H_7	H	$(CH_3)_2NCH_2-CH_2$	5	H	1	223
52	CH_3	$ClCH_2-CH_2$	C_3H_7	H	$(CH_3)_2NCH_2-CH_2$	5	H	1	204
53	CH_3	C_3H_7	C_3H_7	H	2-pyridyl-CH_2-CH_2	5	H	1	199
54	CH_3	C_3H_7	C_3H_7	H	1-imidazolyl-$-(CH_2)_3$	5	H	1	177
55	CH_3	C_3H_7	C_3H_7	H	2,2,6,6-tetramethyl-4-piperidyl	5	H	1	243
56	CH_3	C_3H_7	C_3H_7	H	H_2N-CNH	5	H	1	337-338
57	CH_3	C_3H_7	C_3H_7	H	3-β-D-gluco-pyranosyl	5	H	1	200

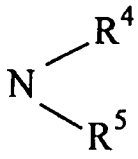
Compound	R^1	R^2	R^3	R^4	R^5	Sulfonamide position	R^6	Method Example	m.p. °C
58	CH_3	C_3H_7	C_3H_7	H		5	H	1	195

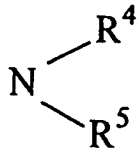
TABLE 3

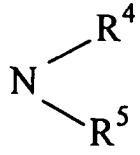
Compound	R^1	R^2	R^3	R^4, R^5 =	Sulfonamide position	R^6	Method Example	m.p. °C
59	CH_3	CH_3	C_2H_5	4-hydroxy-1-piperidyl	5	H	1	267
60	CH_3	C_2H_5	C_3H_7	4-hydroxy-1-piperidyl	5	H	1	219
61	CH_3	C_3H_7	C_2H_5	4-hydroxy-1-piperidyl	5	H	1	241
62	CH_3	C_3H_7	C_3H_7	4-hydroxy-1-piperidyl	5	H	1	227
63	CH_3	$i\text{-}C_3H_7$	C_3H_7	4-hydroxy-1-piperidyl	5	H	1	209
64	CH_3	$HOCH_2\text{-}CH_2$	C_3H_7	4-hydroxy-1-piperidyl	5	H	1	229
65	CH_3	$i\text{-}C_4H_9$	C_3H_7	4-hydroxy-1-piperidyl	5	H	1	241
66	CH_3	$CH_3OCH_2CH_2$	C_3H_7	4-hydroxy-1-piperidyl	5	H	1	219
67	CH_3	$ClCH_2\text{-}CH_2$	C_3H_7	4-hydroxy-1-piperidyl	5	H	1	203
68	CH_3	$CH_3CH_2\text{-}CH(CH_3)CH_2$	C_3H_7	4-hydroxy-1-piperidyl	5	H	1	235
69	CH_3	$(CH_3)_2NCH_2\text{-}CH_2$	C_3H_7	4-hydroxy-1-piperidyl	5	H	1	240

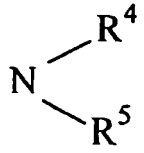
Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
70	CH_3	C_3H_7	C_3H_7	3-carbamoyl-1-piperidyl	5	H	1	255
71	H	C_3H_7	C_3H_7	4-carbamoyl-1-piperidyl	5	H	1	286
72	CH_3	CH_3	C_2H_5	4-carbamoyl-1-piperidyl	5	H	1	289
73	CH_3	C_3H_7	CH_3	4-carbamoyl-1-piperidyl	5	H	1	287
74	CH_3	C_3H_7	C_2H_5	4-carbamoyl-1-piperidyl	5	H	1	288-289
75	CH_3	C_3H_7	C_3H_7	4-carbamoyl-1-piperidyl	5	H	1	279
76	CH_3	C_3H_7	n-C_4H_9	4-carbamoyl-1-piperidyl	5	H	1	254
77	CH_3	n-C_4H_9	C_3H_7	4-carbamoyl-1-piperidyl	5	H	1	283

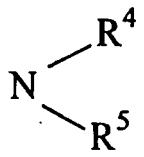
Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
78	n-C_4H_9	n-C_4H_9	C_3H_7	4-carbamoyl-1-piperidyl	5	H	1	170-171
79	CH_3	C_3H_7	C_3H_7	3-carboxy-1-piperidyl	5	H	1	140
80	CH_3	C_3H_7	C_3H_7	4-carboxy-1-piperidyl	5	H	1	261
81	CH_3	C_3H_7	C_3H_7	3-ethoxycarbonyl-1-piperidyl	5	H	1	168
82	CH_3	C_3H_7	C_3H_7	4-ethoxycarbonyl-1-piperidyl	5	H	1	186-187
83	CH_3	C_3H_7	C_3H_7		5	H	1	174
84	H	C_3H_7	C_3H_7	1-piperazinyl	5	H	1	240
85	CH_3	CH_3	C_2H_5	1-piperazinyl	5	H	1	271
86	CH_3	C_3H_7	C_3H_7	1-piperazinyl	5	H	1	198

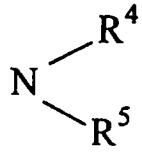
Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
87	HO_2C-CH_2	C_3H_7	C_3H_7	1-piperazinyl	5	H	1	222
88	CH_3	C_3H_7	C_3H_7	3-methyl-1-piperazinyl	5	H	1	190
89	H	C_3H_7	C_3H_7	4-methyl-1-piperazinyl	5	H	1	244
90	CH_3	CH_3	C_2H_5	4-methyl-1-piperazinyl	5	H	1	255
91	CH_3	C_2H_5	C_3H_7	4-methyl-1-piperazinyl	5	H	1	181
92	CH_3	C_3H_7	H	4-methyl-1-piperazinyl	5	H	1	285
93	CH_3	C_3H_7	CH_3	4-methyl-1-piperazinyl	5	H	1	198
94	CH_3	C_3H_7	C_2H_5	4-methyl-1-piperazinyl	5	H	1	174

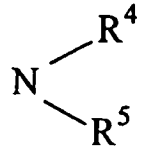
Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
95	CH_3	C_3H_7	C_3H_7	4-methyl-1-piperazinyl	4	H	2	212
96	CH_3	C_3H_7	C_3H_7	4-methyl-1-piperazinyl	5	H	1	189
97	CH_3	C_3H_7	C_3H_7	4-methyl-1-piperazinyl	5	CH_3	3	144
98	CH_3	C_3H_7	n-C_4H_9	4-methyl-1-piperazinyl	5	H	1	225
99	CH_3	C_3H_7	i-C_4H_9	4-methyl-1-piperazinyl	5	H	1	206
100	CH_3	n-C_4H_9	C_2H_5	4-methyl-1-piperazinyl	5	H	1	192
101	CH_3	n-C_4H_9	C_2H_5	4-methyl-1-piperazinyl	5	CH_3	3	144
102	CH_3	i-C_3H_7	C_3H_7	4-methyl-1-piperazinyl	5	H	1	223

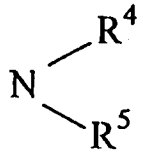
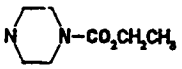
Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
103	CH_3	n-C_4H_9	C_3H_7	4-methyl-1-piperazinyl	5	H	1	155
104	CH_3	i-C_4H_9	C_3H_7	4-methyl-1-piperazinyl	5	H	1	199
105	CH_3	i-C_4H_9	C_3H_7	4-methyl-1-piperazinyl	5	CH_3	3	193
106	CH_3	CH_3CH_2-$CH(CH_3)CH_2$	C_3H_7	4-methyl-1-piperazinyl	5	H	1	131
107	CH_3	cyclo-propyl	C_3H_7	4-methyl-1-piperazinyl	5	H	1	242
108	CH_3	C_6H_5	C_3H_7	4-methyl-1-piperazinyl	5	H	2	235
109	CH_3	cyclo-propyl-CH_2	C_3H_7	4-methyl-1-piperazinyl	5	H	2	190
110	CH_3	cyclo-hexyl-CH_2	C_3H_7	4-methyl-1-piperazinyl	5	H	1	202

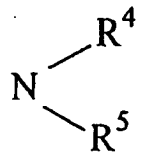
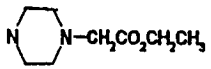
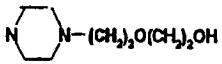
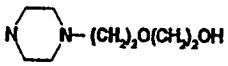
Com-pound	R^1	R^2	R^3		Sulfon-amide position	R^6	Method Example	m.p. °C
111	CH_3	piperonyl	C_3H_7	4-methyl-1-piperazinyl	5	H	2	222
112	CH_3	allyl	C_3H_7	4-methyl-1-piperazinyl	5	H	2	185
113	CH_3	$HOCH_2-CH_2$	C_3H_7	4-methyl-1-piperazinyl	5	H	1	242
114	CH_3	$CH_3OCH_2-CH_2$	C_3H_7	4-methyl-1-piperazinyl	5	H	1	171
115	CH_3	$(CH_3)_2NCH_2-CH_2$	C_3H_7	4-methyl-1-piperazinyl	5	H	1	181
116	CH_3	$(CH_3)_2NCH_2-CH_2-CH_2$	C_3H_7	4-methyl-1-piperazinyl	5	H	1	197
117	CH_3	$ClCH_2-CH_2$	C_3H_7	4-methyl-1-piperazinyl	5	H	1	176
118	CH_3	$ClCH_2CH_2-CH_2$	C_3H_7	4-methyl-1-piperazinyl	5	H	1	170

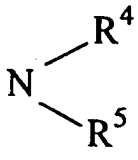
Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
119	C_2H_5	C_3H_7	C_3H_7	4-methyl-1-piperazinyl	5	H	1	175
120	n-C_4H_9	n-C_4H_9	C_3H_7	4-methyl-1-piperazinyl	5	H	1	140
121	HO_2C-CH_2	C_3H_7	C_3H_7	4-methyl-1-piperazinyl	5	H	1	254
122	CH_3	C_3H_7	C_3H_7	2,5-dimethyl-1-piperazinyl	5	H	1	230
123	CH_3	C_3H_7	C_3H_7	3,5-dimethyl-1-piperazinyl	5	H	1	230
124	CH_3	C_3H_7	C_3H_7	4-ethyl-1-piperazinyl	5	H	1	145
125	CH_3	i-C_3H_7	C_3H_7	4-ethyl-1-piperazinyl	5	H	1	202
126	CH_3	i-C_4H_9	C_3H_7	4-ethyl-1-piperazinyl	5	H	1	180
127	CH_3	C_3H_7	C_3H_7	4-propyl-1-piperazinyl	5	H	1	161

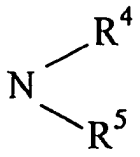
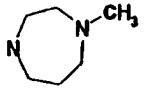
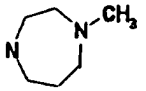
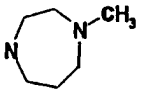
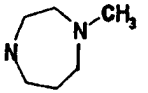
Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
128	H	C_3H_7	C_3H_7	4-(2-hydroxyethyl) -1-piperazinyl	5	H	1	261
129	CH_3	C_2H_5	C_3H_7	4-(2-hydroxyethyl) -1-piperazinyl	5	H	1	204
130	CH_3	CH_3	C_2H_5	4-(2-hydroxyethyl) -1-piperazinyl	5	H	1	270
131	CH_3	C_3H_7	CH_3	4-(2-hydroxyethyl) -1-piperazinyl	5	H	1	225
132	CH_3	C_3H_7	C_3H_7	4-(2-hydroxyethyl) -1-piperazinyl	4	H	1	160
133	CH_3	C_3H_7	C_3H_7	4-(2-hydroxyethyl) -1-piperazinyl	5	H	1	189
134	CH_3	C_3H_7	C_3H_7	4-(2-hydroxyethyl) -1-piperazinyl	5	CH_3	3	107-108

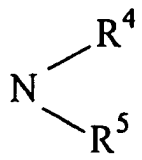
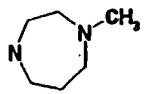
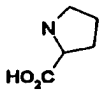
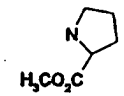
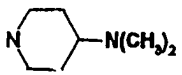
Com-pound	R^1	R^2	R^3		Sulfon-amide position	R^6	Method Example	m.p. °C
135	CH_3	C_3H_7	n-C_4H_9	4-(2-hydroxyethyl) -1-piperazinyl	5	H	1	180
136	CH_3	C_3H_7	i-C_4H_9	4-(2-hydroxyethyl) -1-piperazinyl	5	H	1	204
137	CH_3	n-C_4H_9	C_2H_5	4-(2-hydroxyethyl) -1-piperazinyl	5	H	1	200
138	CH_3	n-C_4H_9	C_2H_5	4-(2-hydroxyethyl) -1-piperazinyl	5	CH_3	3	140-142
139	CH_3	i-C_3H_7	C_3H_7	4-(2-hydroxyethyl) -1-piperazinyl	5	H	1	210
140	CH_3	i-C_4H_9	C_3H_7	4-(2-hydroxyethyl) -1-piperazinyl	5	H	1	183
141	CH_3	i-C_4H_9	C_3H_7	4-(2-hydroxyethyl) -1-piperazinyl	5	CH_3	3	190

Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
142	CH_3	CH_3CH_2-$CH(CH_3)CH_2$	C_3H_7	4-(2-hydroxyethyl)-1-piperazinyl	5	H	1	177
143	CH_3	C_6H_5	C_3H_7	4-(2-hydroxyethyl)-1-piperazinyl	5	H	2	265
144	C_2H_5	C_3H_7	C_3H_7	4-(2-hydroxyethyl)-1-piperazinyl	5	H	1	168
145	CH_3	$ClCH_2CH_2$-CH_2	C_3H_7	4-(2-hydroxyethyl)-1-piperazinyl	5	H	1	166
146	HO_2C-CH_2	C_3H_7	C_3H_7	4-(2-hydroxyethyl)-1-piperazinyl	5	H	1	217
147	CH_3	C_3H_7	C_3H_7		5	H	1	213-214

Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
148	CH_3	C_3H_7	C_3H_7		5	H	1	161
149	CH_3	C_3H_7	C_3H_7		5	H	1	137
150	HO_2C-CH_2	C_3H_7	C_3H_7		5	H	1	145
151	CH_3	CH_3	C_2H_5	4-morpholinyl	5	H	1	261
152	CH_3	C_3H_7	C_2H_5	4-morpholinyl	5	H	1	212-214
153	CH_3	C_3H_7	C_3H_7	4-morpholinyl	5	H	1	208
154	CH_3	$n-C_4H_9$	C_3H_7	4-morpholinyl	5	H	1	184

Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
155	n-C_4H_9	n-C_4H_9	n-C_4H_9	4-morpholinyl	5	H	1	132
156	CH_3	cyclo-propyl-CH_2	C_3H_7	4-morpholinyl	5	H	2	192
157	CH_3	cyclo-hexyl-CH_2	C_3H_7	4-morpholinyl	5	H	1	233
158	CH_3	benzyl	C_3H_7	4-morpholinyl	5	H	2	218
159	CH_3	piperonyl	C_3H_7	4-morpholinyl	5	H	2	202
160	CH_3	i-C_3H_7	C_3H_7	4-morpholinyl	5	H	1	228
161	CH_3	i-C_4H_9	C_3H_7	4-morpholinyl	5	H	1	204
162	CH_3	CH_3CH_2-$CH(CH_3)CH_2$	C_3H_7	4-morpholinyl	5	H	1	205

Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
163	CH_3	C_3H_7	C_3H_7		4	H	2	204
164	CH_3	C_3H_7	C_3H_7		5	H	1	138
165	CH_3	i-C_4H_9	C_3H_7		5	H	1	179
166	CH_3	CH_3CH_2- $CH(CH_3)CH_2$	C_3H_7		5	H	1	149

Compound	R^1	R^2	R^3		Sulfonamide position	R^6	Method Example	m.p. °C
167	HO_2C-CH_2	C_3H_7	C_3H_7		5	H	1	234
168	CH_3	C_3H_7	C_3H_7		5	H	1	220
169	CH_3	C_3H_7	C_3H_7		5	H	1	189
170	CH_3	C_3H_7	C_3H_7		5	H	1	174
171	CH_3	C_3H_7	C_2H_5	3-amino-1-pyrazolyl	5	H	1	247
172	CH_3	C_3H_7	C_3H_7	3-amino-1-pyrazolyl	5	H	1	224

The Examples 4 and 5 illustrate pharmaceutical compositions according to the present invention and procedure for their preparation.

EXAMPLE 4

50,000 capsules each containing 100 mg of 8-[2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-methyl-3-propyl-3,7-dihydropurine-2,6-dione (active ingredient) were prepared according to the following formulation:

Active ingredient	5 Kg
Lactose monohydrate	10 Kg
Colloidal silicone dioxide	0.1 Kg
Corn starch	1 Kg
Magnesium stearate	0.2 Kg

Procedure

The above ingredients were sieved through a 60 mesh sieve, and were loaded into a suitable mixer and filled into 50,000 gelatine capsules.

EXAMPLE 5

50,000 Tablets each containing 50 mg of the 8-[2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-methyl-3-propyl-3,7-dihydropurine-2,6-dione (active ingredient) were prepared from the following formulation:

Active ingredient	2.5 Kg
Microcrystalline cellulose	1.95 Kg
Spray dried lactose	9.95 Kg
Carboxymethyl starch	0.4 Kg
Sodium stearyl fumarate	0.1 Kg
Colloidal silicon dioxide	0.1 Kg

Procedure

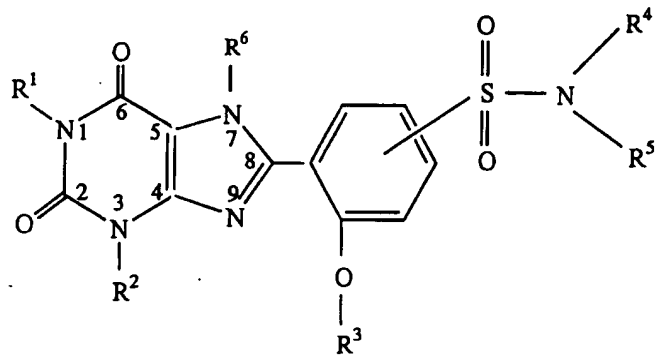
All the porders were passed through a screen with an aperture of 0.6 mm, then mixed in a suitable mixer for 20

minutes and compressed into 300 mg tablets using 9 mm disc and flat bevelled punches. The disintegration time of the tablets was about 3 minutes.

5

CLAIMS

1. A compound of formula (I)



(I)

wherein:

R^1, R^2 and R^3 each independently represent a hydrogen atom or an alkenyl, alkynyl, cycloalkyl or alkylcarbamoyl group or an alkyl group which may be unsubstituted or substituted by one or more halogen atoms or hydroxy, alkoxyl, cycloalkyl, alkylthio, amino, mono- or di-alkylamino, cycloalkyl, oxo, hydroxycarbonyl, alkoxycarbonyl, carbamoyl or alkylcarbamoyl groups, or a benzyl or phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, hydroxy, alkylenedioxy, alkoxy, amino, mono- or di-alkylamino, nitro, cyano or trifluoromethyl groups;

either R^4 and R^5 together with the nitrogen atom to which they are attached form a 3 to 7-membered ring comprising a total of from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted by one or two halogen atoms or hydroxy, carbamoyl, hydroxycarbonyl, alkoxycarbonyl, amino, mono- or di-alkylamino groups or one or two alkyl groups which may be unsubstituted or substituted by one or more hydroxy, alkoxy, hydroxyalkoxy, hydroxycarbonyl, alkoxycarbonyl, amino or mono- or di-alkylamino groups, or

R^4 is as defined for R^1 and R^5 represents an alkenyl, alkynyl, cycloalkyl, mono-or di-alkylamino, alkylcarbamoyl, aminocarboiminoyl group or an alkyl group substituted by one

or more halogen atoms or hydroxy, alkoxy, cycloalkyl, alkylthio, oxo, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, amino or mono- or di-alkylamino groups; or R^5 represents a group of formula

$$-(CH_2)_n-R^7$$

wherein n is an integer from 0 to 4 and R^7 represents a 3 to 7-membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted by one or more halogen atoms or hydroxy, phenyl, alkoxycarbonyl, amino, mono-alkylamino, di-alkylamino or hydroxycarbonyl groups or one or more alkyl groups which may be unsubstituted or substituted by one or more halogen atoms or hydroxy, phenyl, alkoxycarbonyl, amino, mono-or di-alkylamino or hydroxycarbonyl groups;

R^6 represents a hydrogen atom or an alkyl group;

and the $-SO_2NR^4R^5$ group is in the 4 or 5 position on the phenyl group;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1, R^2 and R^3 each independently represent an unsubstituted alkyl, monosubstituted alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl, phenyl, benzyl or substituted benzyl group.

3. A compound according to claim 2 wherein R^1, R^2 and R^3 each independently represent a methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, 2-chloroethyl, 2-hydroxyethyl, 2-methoxyethyl, 2-dimethylaminoethyl, 3-chloropropyl, 3-dimethylaminopropyl, 2-methyl-n-butyl, hydroxycarbonylmethyl, cyclopropyl, cyclopropylmethyl, cyclohexylmethyl, allyl, phenyl, benzyl or piperonyl group.

4. A compound according to any one of the preceding claims wherein R^4 represents a hydrogen atom or a substituted or unsubstituted alkyl group.

5. A compound according to claim 4 wherein R^4 represents a hydrogen atom, a methyl group or a hydroxyethyl group.

6. A compound according to any one of the preceding claims wherein R^5 represents a C_{1-6} alkyl group substituted by one or more halogen atoms or hydroxy, alkoxy, cycloalkyl, alkylthio, oxo, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, amino, mono- or di-alkylamino groups, or R^5 represents a group of formula

$$-(CH_2)_n-R^7$$

wherein n is an integer from 0 to 4 and R^7 represents a 3 to 7-membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring may be unsubstituted or substituted by one or more halogen atoms or hydroxy, phenyl, alkoxycarbonyl, amino, mono- or di-alkylamino or hydroxycarbonyl groups or more alkyl groups which may be substituted or substituted by one or more halogen atoms or hydroxy, phenyl, alkoxycarbonyl, amino, mono-or di-alkylamino or hydroxycarbonyl groups.

7. A compound according to claim 6 wherein R^5 represents a 2-hydroxyethyl, 2-dimethylaminoethyl, propargyl, hydroxycarbonylmethyl, methoxycarbonylmethyl, 2,3-dihydroxy-n-propyl, N-acetyl-2-aminoethyl, carbamoylmethyl, cyclopentyl, pyridyl, pyridylmethyl, pyridylethyl, imidazolylpropyl, N-piperidylethyl, methylpiperidyl, 2,2,6,6-tetramethylpiperidyl, benzylpiperidyl, N-methyl-4-phenylpiperidyl-4-methyl, N-methyl-4-hydroxypiperidyl-4-methyl, N-benzyl-4-hydroxypiperidyl-4-methyl, N-benzyl-3-hydroxypiperidyl-3-methyl, N-ethoxycarbonyl-4-hydroxypiperidyl-4-methyl, N-methylpyrrolidinyl-2-ethylene, 3-β-D-glucopyranosyl, 2,2-cyclohexylidine-2-ethylaminoethyl, N-morpholinylethyl, N-morpholinylpropyl, 2-tetrahydrofurylmethyl, methylpiperazinyl, quinuclidinyl, amidino, triazolyl or tetrazolyl group.

8. A compound according to any one of claims 1 to 3 wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a 5, 6 or 7-membered ring comprising a total of from 1 to 4 heteroatoms selected from nitrogen,

oxygen and sulphur, which ring may be unsubstituted or substituted by one or two halogen atoms or hydroxy, carbamoyl, hydroxycarbonyl, alkoxycarbonyl, amino or mono- or di-alkylamino groups or one or two alkyl groups which may be unsubstituted or substituted by one or more hydroxy, alkoxy, hydroxyalkoxy, amino or mono- or di-alkylamino groups.

9. A compound according to claim 8 wherein the 5, 6 or 7-membered ring comprising a total of from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur is a substituted or unsubstituted piperidyl, piperazinyl, morpholinyl, diazacycloheptyl, pyrrolidinyl or pyrazolyl group.

10. A compound according to claim 9 wherein the 5, 6 or 7-membered ring comprising a total of from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur is a 4-hydroxypiperidyl, 3-carbamoylpiperidyl, 4-carbamoylpiperidyl, 3-carboxypiperidyl, 4-carboxypiperidyl, 3-ethoxycarbonylpiperidyl, 4-ethoxycarbonylpiperidyl, 4-dimethylaminopiperidyl, 4-(2-dimethylaminoethyl)-4-methylpiperidyl, piperazinyl, 3-methylpiperazinyl, 4-methylpiperazinyl, 2,5-dimethylpiperazinyl, 3,5-dimethylpiperazinyl, 4-ethylpiperazinyl, 4-propylpiperazinyl, 4-hydroxyethylpiperazinyl, 4-ethoxycarbonylpiperazinyl, 4-ethoxycarbonylmethylpiperazinyl, 4-(2-hydroxyethoxy)ethylpiperazinyl, morpholinyl, 4-methyl-1,4-diazacycloheptyl, 2-hydroxycarbonylpyrrolidinyl, 2-methoxycarbonylpyrrolidinyl or aminopyrazolyl group.

11. A compound according to any one of the preceding claims wherein R^6 represents a hydrogen atom or a methyl group.

12. A compound according to any one of the preceding claims wherein the $-SO_2NR^4R^5$ group is on the 5-position of the phenyl group.

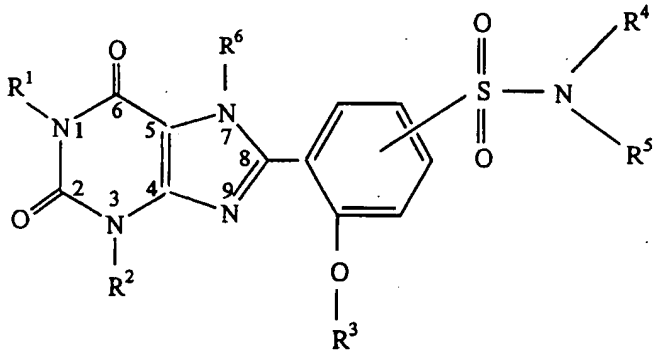
13. 3-(3-butyl-1-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-4-propoxy-*N*-pyridin-4-ylbenzenesulfonamide,

4-ethoxy-3-(1-methyl-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-*N*-(1*H*-[1,2,4]triazol-3-yl)benzenesulfonamide,

3-(1-methyl-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-8-

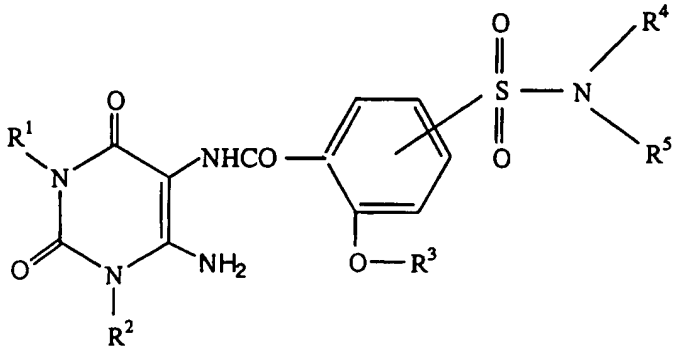
yl)-4-propoxy-*N*-(1*H*-[1,2,4]triazol-3-yl)benzenesulfonamide,
1-[3-(1-methyl-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-8-yl)-4-propoxybenzenesulfonyl]piperidine-4-carboxylic acid amide,
1-methyl-8-[5-(4-methylpiperazine-1-sulfonyl)-2-propoxyphenyl]-3-propyl-3,7-dihydropurine-2,6-dione,
3-butyl-1-methyl-8-[5-(morpholine-4-sulfonyl)-2-propoxyphenyl]-3,7-dihydropurine-2,6-dione,
8-{5-[4-(2-hydroxyethyl)piperazine-1-sulfonyl]-2-propoxyphenyl}-1-methyl-3-propyl-3,7-dihydropurine-2,6-dione, and
1-methyl-8-[5-(piperazine-1-sulfonyl)-2-propoxyphenyl]-3-propyl-3,7-dihydropurine-2,6-dione;
or a pharmaceutically acceptable salt thereof.

14. A process for the preparation of a compound of formula (I)



(I)

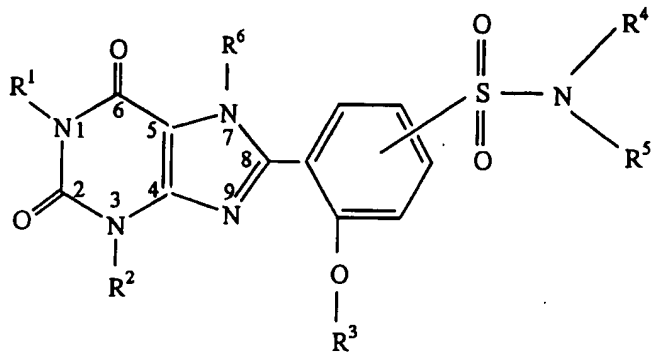
wherein R^1, R^2, R^3, R^4, R^5 and R^7 are as defined in claim 1 and R^6 is hydrogen, which process comprises cyclisation of a uracil compound of formula (II)



(II)

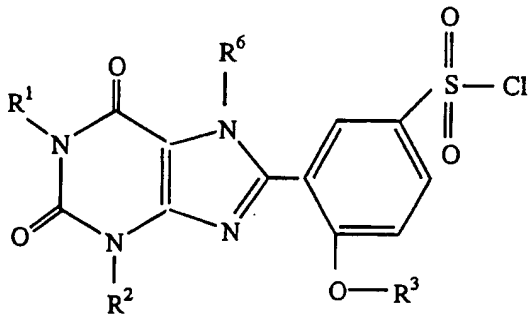
wherein R^1, R^2, R^3, R^4, R^5, and R^7 are as defined above.

15. A process for the preparation of a compound of formula (I)



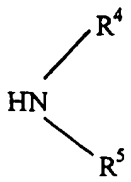
(I)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in claim 1 provided that if R^6 is an alkyl group any of R^1, R^2 or R^3 are not hydrogen atoms, and the $-SO_2NR^4R^5$ group is on the 5-position of the phenyl group, which process comprises reacting a compound of formula (IXa)



(IXa)

wherein R^1, R^2, R^3 and R^6 are as defined above with an amine of formula (X)



(X)

wherein R^4 and R^5 are as defined above, in the presence of an organic base.

16. A composition comprising a compound according to

any one of claims 1 to 13 or pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or diluent.

17. A compound according to any one of claims 1 to 13 or pharmaceutically acceptable salt thereof or a composition according to claim 15 for use in a method of treatment of the human or animal body.

18. Use of a compound according to any one of claims 1 to 13 or pharmaceutically acceptable salt thereof or a composition according to claim 16 for the manufacture of a medicament for the treatment of angina, hypertension, congestive heart failure, stroke, asthma, bronchitis, male erectile dysfunction, female sexual dysfunction, glaucoma or irritable bowel syndrome.

19. A method for treating angina, hypertension, congestive heart failure, stroke, asthma, bronchitis, male erectile dysfunction, female sexual dysfunction, glaucoma or irritable bowel syndrome which comprises administering to a human or animal subject in need of treatment an effective amount of a compound according to claim 1 or pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Intern ·onal Application No
PCl, cP 99/03644

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D473/04 C07H13/00 A61K31/52 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 722 929 A (AUSTEL V ET AL) 2 February 1988 (1988-02-02) cited in the application * the whole document, particularly examples 29, 49, 50, 90, 91 and 95 *	1-6,11, 14-17
A	EP 0 352 960 A (SMITH KLINE & FRENCH LABORATORIES LIMITED) 31 January 1990 (1990-01-31) the whole document	1,17-19
A	WO 94 00453 A (PFIZER LIMITED ET AL) 6 January 1994 (1994-01-06) the whole document	1,17-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 September 1999	20/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir ıational application No.
PCT/EP 99/03644

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

formation on patent family members

Interr 'onal Application No
PCT/EP 99/03644

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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